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Distribution of emphysema in heavy smokers: Impact on pulmonary function

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Summary
Purpose: To investigate impact of distribution of computed tomography (CT) emphysema on severity of airflow limitation and gas exchange impairment in current and former heavy smokers participating in a lung cancer screening trial.
Materials and Methods: In total 875 current and former heavy smokers underwent baseline low-dose CT (30 mAs) in our center and spirometry and diffusion capacity testing on the same day as part of the Dutch–Belgian Lung Cancer Screening Trial (NELSON). Emphysema was quantified for 872 subjects as the number of voxels with an apparent lowered X-ray attenuation coefficient. Voxels attenuated <-950 HU were categorized as representing severe emphysema (ES950), while voxels attenuated between -910 HU and -950 HU represented moderate emphysema (ES910). Impact of distribution on severity of pulmonary function impairment was investigated with logistic regression, adjusted for total amount of emphysema.
Results: For ES910 an apical distribution was associated with more airflow obstruction and gas exchange impairment than a basal distribution (both $p < 0.01$). The FEV_1/FVC ratio was 1.6% (95% CI 0.42% to 2.8%) lower for apical predominance than for basal predominance, for $Tlco/V_A$ the difference was 0.12% (95% CI 0.076–0.15%). Distribution of ES950 had no impact on FEV_1/FVC ratio, while an apical distribution was associated with a 0.076% (95% CI 0.038–0.11%) lower $Tlco/V_A$ ($p < 0.001$).

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Conclusion: In a heavy smoking population, an apical distribution is associated with more severe gas exchange impairment than a basal distribution; for moderate emphysema it is also associated with a lower FEV_1/FVC ratio. However, differences are small, and likely clinically irrelevant.

Introduction

Chronic obstructive pulmonary disease (COPD) is the most frequent chronic disease in developed countries and is predicted to be the third cause of death in 2020.[1] COPD is a multicomponent disease comprising a combination of small airways disease (bronchiolitis) and parenchyma destruction (emphysema)[2] and characterized by airflow limitation assessed by spirometry. One of the limitations of spirometry, but also of diffusion capacity testing, is its inherent global character, while distribution of disease may be an important factor in the severity and progression of airflow limitation [3] and gas exchange impairment. Computed tomography (CT) can non-invasively provide anatomical information about the location and the extent of emphysema and has been shown to correlate well with histology.[4–7] Due to its non-invasive character it is also an attractive method to study changes in emphysema and airway disease over time. The National Emphysema Treatment Trial (NETT) has shown that not the extent of emphysema, but the distribution of emphysema is one of the predicting factors for the survival rate of severe COPD patients.[8]

Previous studies have suggested that subjects with a similar degree of parenchyma destruction can show different degrees of airflow limitation and gas exchange impairment dependent on the location of the damage in the lungs.[9] The impact of these patterns of emphysema distribution has been investigated in patients with α_1-antitrypsin deficiency (AATD) suffering from severe emphysema,[9] but these results cannot easily be extrapolated to smoking related COPD. An earlier study among unselected smokers could only demonstrate an association between distribution pattern (i.e. apical or basal predominance of emphysema) and pulmonary function for subjectively (i.e. visually) quantified extent of lung destruction, but not for automated quantified emphysema.[10] However, the sample size of this study was relatively small and only a part of the lungs was analyzed with the automated method. We hypothesized that we would be able to demonstrate the impact of emphysema distribution on pulmonary function parameters studying a large sample of heavy smokers with overlapping CT data.

The aim the current study was to investigate the impact of emphysema distribution on severity of airflow limitation and gas exchange impairment in a population of current and former heavy smokers participating in a lung cancer screening trial.

Material and methods

Subjects

The NELSON-trial (Nederlands-Leuvens longScreenings ONderzoek) is a population based randomized Dutch—Belgian multi-center lung cancer screening trial, studying current and former heavy smokers. The trial was approved by the Dutch ministry of health and by the ethics committee of each participating hospital. Selection of subjects for the trial was performed by sending out a questionnaire about smoking history and other health-related issues to people between 50 and 75 years of age, living in the areas around the participating centers.[11] Subjects, who met the inclusion criterion of a minimum of 16 cigarettes/day for 25 years or 11 cigarettes/day for 30 years and gave written informed consent, were equally randomized to either the screening arm or the control arm. Before inviting eligible subjects, persons with a moderate or poor self-reported health status who were unable to climb two flights of stairs were excluded from participation.

From 2997 subjects who underwent baseline screening in our hospital, about one out of three was randomly selected for pulmonary function testing on the same day. This was done due to logistic considerations.

Pulmonary function tests

Pulmonary function tests (PFT) included forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) with a pneumotachograph and assessment of diffusion capacity (Tlco), according to ERS guidelines.[12] No reversibility testing was performed. Diffusing capacity measurements were performed after spirometry. The inhalation mixture contained 0.3% CO and 10% He with balance air. Results were expressed as percentages of predicted values.

CT scanning and calculation emphysema scores

CT scans were performed on a multidetector-row scanner (Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH, USA). All scans were realized within 12 s, in spiral mode with 16×0.75 mm collimation, 1.0 mm reconstruction thickness with 0.7 mm increment, without contrast-injection. Exposure settings were 30 mAs at 120 kVp for subjects weighing $\leq$80 kg or 30 mAs at 140 kVp for those weighing over 80 kg, without dose modulation. Scans were performed in end-inspiration.

Scans were transferred to a digital workstation with in-house developed software (ImageXplorer (iX) Image Sciences Institute, Utrecht, The Netherlands).[13] A fully automated region-growing program segmented both lungs starting from the trachea and including all connected areas with attenuated below -500 HU. In a next step, airways were segmented and excluded. The algorithm is similar to the one described by Hu et al.[14] Finally, segmented lungs were subjected to a noise filter.[15] The extent of emphysema was estimated using the threshold technique quantifying the percent of the total lung voxels with an apparent

X-ray attenuation value below to predefined thresholds (−950 Hounsfield units (HU) and −910 HU). Lung areas with an attenuation between −910 HU and −950 HU (ES_{910}) were considered to represent moderate emphysema, while lung volume with an attenuation below −950 HU (ES_{950}) were considered to represent severe emphysema.[4,8] Emphysema scores (ES) were given as percentage of total lung volume in a range from 0% to 100%.

Distribution of emphysema and statistics

We calculated means, standard deviations (SD) and 95% confidence intervals (CI) for normal distributed parameters and medians and interquartile ranges for non-normal distributed parameters.

The lungs were divided into three parts with equal volumes (top, middle and lower part) and ES_{910} and ES_{950} were calculated for each part. Since none of the subjects showed the middle part to be the main area for emphysematous changes, we compared the extent of emphysema in the top and lower parts. Distribution of emphysema for both ES_{910} and ES_{950} was assessed by subtracting the extent of emphysema in the lower part from the extent of emphysema in the top part of the lungs. A positive result was considered a predominant apical distribution; a negative result was considered a predominant basal distribution.

Impact of distribution pattern on pulmonary function parameters was assessed via analysis of variance, adjusted for differences in ES_{910}/ES_{950}, sex, age and height in both distribution groups. Analysis was repeated on a subgroup of subjects including only subjects with $FEV_1/FVC < 0.7$.

Since many subjects had an apical predominance for ES_{910} and a basal predominance for ES_{950}, while their pulmonary function results are independent of the applied density threshold, we performed the analyses again including only those subjects who had an apical predominance or a basal predominance for both levels of lung destruction and therefore a consistent distribution pattern.

All statistics were calculated with SPSS statistical software package version 15.0 (SPSS, Chicago, Ill.). *p*-Values <0.05 were considered significant.

Results

Subjects

Eight hundred and seventy-five subjects (50—74 years, mean 62 years), 453 current smokers and 422 former smokers completed all tests. Three subjects were excluded from further analysis, because the software failed to calculate their emphysema scores. Since the NELSON trial started enrollment with only male (former) smokers, the vast majority of subjects (828; 95%) in the current study were male. Characteristics of the study subjects are shown in Table 1 for the total study population and in Table 2 split by distribution pattern.

In total 625 subjects (72%) had a consistent distribution pattern for both levels of lung parenchyma destruction, including 179 (29%) subjects with an apical predominance and 445 (71%) subjects with a basal predominance. These 625 subjects had a difference in emphysema scores between the upper and lower parts of the lungs of −2.5% (±13.4%) for ES_{910} and 0.91% (±6.2%) for ES_{950}. For those subjects who had their distribution pattern to differ dependent on the applied density threshold ($n = 247$), differences between emphysema scores in the upper parts of the lungs and emphysema scores in the lower parts of the lungs were smaller: −0.59% (±5.25%) for ES_{910} ($p = 0.005$) and 0.01% (±1.29%) for ES_{950} ($p = 0.001$).

Moderate emphysema

Mean extent of moderate emphysema was 13.9% (±14.1%) ranging from 0.0% to 67.0%. ES_{910} was not related to smoking history in pack-years or to FEV_1/FVC for the total study population, while it was weakly related to $Tlco/V_A$ ($r = -0.31$; $p < 0.001$). For subjects with a FEV_1/FVC ratio <0.7 only, emphysema and FEV_1/FVC were weakly associated ($r = -0.39$, $p < 0.001$).

Two hundred and fifty-five subjects (29%) had a predominant apical distribution pattern of moderate emphysema; 617 (71%) subjects had a predominant basal

Table 1

Item	
ES_{910}	
Mean	8.6%
SD	2.7—22.0%
ES_{950}	
Mean	0.12%
SD	0.04—0.4%
Age (years)	
Mean	60.0
SD	5.5
Height (cm)	
Mean	177.7
SD	7.5
Pack-years	
Mean	40.7
SD	16.1
FEV_1	
Mean	98.5%
SD	87.3—109.2%
Vital capacity	
Mean	105.6%
SD	97.0—114.3%
FEV_1/FVC	
Mean	96.0%
SD	87.7—101.8%
$Tlco/V_A$ (% predicted)	
Median	83.2%
Intequartile range	71.8—93.5%

Descriptive statistics for the total study population shown as mean values and standard deviations (SD). Emphysema scores represent percentages of total lung volume. All lung function parameters are expressed as percentage of the predicted value.

Table 2

	Apical predominance	Basal predominance
Moderate emphysema		
Number of subjects	255	617
Emphysema score		
Mean	14.6%	7.2%
SD	4.4–30.1%	2.3–18.5%
Age (years)		
Mean	60.3	59.9
SD	5.6	5.5
Height (cm)		
Mean	176.7	178.1
SD	8.1	7.2
Pack-years		
Mean	41.7	41.0
SD	15.8	16.3
FEV_1 (% predicted)		
Median	98.5%	98.6%
Interquartile range	85.1–109.2%	87.8–109.2%
Vital capacity (% predicted)		
Median	108.9%	104.7%
Interquartile range	99.6–118.3%	13.9%
FEV_1/FVC (% predicted)		
Median	92.9%	97.0%
Interquartile range	84.4–99.9%	89.2–102.3%
Tlco/V_A (% predicted)		
Median	76.5%	104.7%
Interquartile range	64.0–88.0%	96.0–113.2%
Severe emphysema		
Number of subjects	315	521
Emphysema score		
Mean	0.1%	0.12%
SD	0.02–0.8%	0.05–0.31%
Age (years)		
Mean	59.9	60.1
SD	5.3	5.6
Height (cm)		
Mean	177.2	177.9
SD	8.0	7.2
Pack-years		
Mean	42.4	40.5
SD	15.4	16.7
FEV_1 (% predicted)		
Median	98.2%	98.4%
Interquartile range	87.2–108%	87.6–110%
Vital capacity (% predicted)		
Median	104%	107%
Interquartile range	96.1–114.0%	97.1–115%
FEV_1/FVC (% predicted)		
Median	96.9%	95.4%
Interquartile range	87.5–103%	87.7–101%
Tlco/V_A (% predicted)		
Median	80.3%	84.8%
Interquartile range	67.8–90.9%	75.2–94.1%

Descriptive statistics shown as mean values and standard deviations (SD) for normal distributed data and as median and interquartile range for non-normal distributed ones, broken down by distribution pattern. Emphysema scores represent percentages of total lung volume. All lung function parameters are expressed as percentage of the predicted value. Moderate emphysema is detected as lung volume with an attenuation between −950 HU and −910 HU; severe emphysema is detected as lung volume with an attenuation below −950 HU.

distribution. An apical predominance of moderate emphysema was associated with a lower FEV_1/FVC ratio compared to basal distribution ($p < 0.001$). Subjects with an apical predominance showed a FEV_1/FVC ratio that was 1.60% (95% CI 0.50–3.28%) lower than the FEV_1/FVC ratio in subjects with a basal predominance. An apical predominance was also associated with a slightly lower Tlco/V_A compared to a basal predominance ($p < 0.001$); subjects with an apical predominance showed a ratio that was 0.12% (95% CI 0.076–0.15%) lower than the Tlco/V_A ratio in subjects with a basal predominance.

The subgroup of 314 subjects with a FEV_1/FVC ratio <0.7 showed no impact of emphysema distribution pattern on FEV_1/FVC ($p = 0.11$), but also in this subgroup an apical predominance was also associated with a lower Tlco/V_A compared to a basal predominance ($p < 0.001$); subjects with an apical predominance showed a ratio that was 0.15% (95% CI 0.089–0.20%) lower than the Tlco/V_A ratio in subjects with a basal predominance.

In the subgroup of 625 subjects with the same distribution pattern for both levels of lung parenchyma destruction, an apical distribution was significantly associated with a lower FEV_1/FVC ratio ($p < 0.001$); subjects with an apical predominance had a ratio that was 3.2% (95% CI 1.5–5.0%) lower than in those with a basal predominance. An apical distribution was also significantly associated with a lower Tlco/V_A ratio ($p < 0.001$), being 0.17% (95% CI 0.13–0.21%) lower compared to the Tlco/V_A ratio in subjects with a basal predominance.

Severe emphysema

Mean extent of severe emphysema was 0.86% (±2.9%) ranging from 0.0% to 30.7%. ES_{950} was not related to smoking history in pack-years or to FEV_1/FVC for the total study population, while it was weakly related to Tlco/V_A ($r = -0.35$; $p < 0.001$). For subjects with a FEV_1/FVC ratio <0.7 only, FEV_1/FVC was moderately associated to extent of emphysema ($r = -0.45$, $p < 0.001$) Three hundred and fifty-one subjects (40%) had an apical prominent

distribution pattern of moderate emphysema, 521 subjects (60%) had a predominant basal distribution.

No impact of distribution of severe emphysema on FEV_1/FVC could be detected. For diffusion capacity, an apical distribution was associated with a lower Tlco/V_A ratio ($p < 0.001$) compared to a basal distribution. Subjects with an apical predominance showed a Tlco/V_A ratio, which was 0.076% (95% CI 0.038–0.11%) lower than the ratio in subjects with a basal distribution pattern.

The subgroup of 314 subjects with a FEV_1/FVC ratio <0.7 showed again no impact of emphysema distribution pattern on FEV_1/FVC ($p = 0.71$), but an apical predominance was also associated with a lower Tlco/V_A compared to a basal predominance ($p < 0.001$); subjects with an apical predominance showed a ratio that was 0.13% (95% CI 0.076–0.18%) lower than the Tlco/V_A ratio in subjects with a basal predominance.

Only in the subgroup of subjects with the same distribution pattern for both levels of lung parenchyma destruction, an apical distribution was significantly associated with a lower FEV_1/FVC ratio ($p = 0.03$); subjects with an apical predominance had a ratio that was 1.7% (95% CI 0.16–3.2%) lower than in those with a basal predominance. In this subgroup, an apical distribution was also significantly associated with a lower Tlco/V_A ratio ($p < 0.001$), with a Tlco/V_A ratio that was 0.14% (95% CI 0.09–0.18%) lower in subjects with an apical predominance than in those with a basal predominance.

Fig. 1 shows two subjects with a similar extent of CT emphysema, but with different distributions and spirometry results.

Discussion

In this study we studied a large sample of relatively healthy current and former heavy smokers with overlapping 1.0 mm thin CT images to investigate the impact of emphysema distribution on lung function parameters. We used two density thresholds commonly used to estimate the extent of CT emphysema and reported that the chosen density threshold had only limited impact on the results. Our results also showed that in these relatively healthy current and former heavy smokers, the emphysema distribution pattern has a significant, but small and therefore likely clinically irrelevant, impact on lung function parameters. By analyzing only subjects with a FEV_1/FVC ratio <0.7, the outcome didn't show major changes and can therefore not be explained by the large number of subjects with normal lung function parameters. When analyzing only those subjects with a consistent distribution pattern for both levels of lung parenchyma destruction and thereby excluding subjects with a more homogeneous distribution pattern, the impact of distribution pattern became slightly clearer, but it remained relatively small.

COPD is a multicomponent disease compromising parenchyma destruction (emphysema) and large and small airways disease.[2] We only investigated lung destruction, not airway wall thickness, in a relatively healthy study group with on average a low extent of lung destruction and didn't show any correlation between the extent of destructed lung tissue and severity of airway obstruction, irrespective of the applied density threshold. This lack of correlation could be caused by the narrow range of spirometry results, but it is also possible that the severity of airway obstruction in the investigated population with early stages of COPD was mainly determined by the extent of airways disease.

An impact of distribution pattern was to be expected since both ventilation and perfusion of the lungs is not equally distributed throughout the lungs. Both ventilation and blood flow per unit volume decrease from the bottom to the top of the upright lung. However, the changes for blood flow are more marked than those for ventilation. Destruction of lung tissue in the upper zones will therefore result in a greater mismatch of ventilation and perfusion than destruction of lung tissue in than lower zones, which explains the worse diffusion capacity for subjects with apical predominant destruction compared to subjects with the same extent of emphysema, but basal predominant disease.

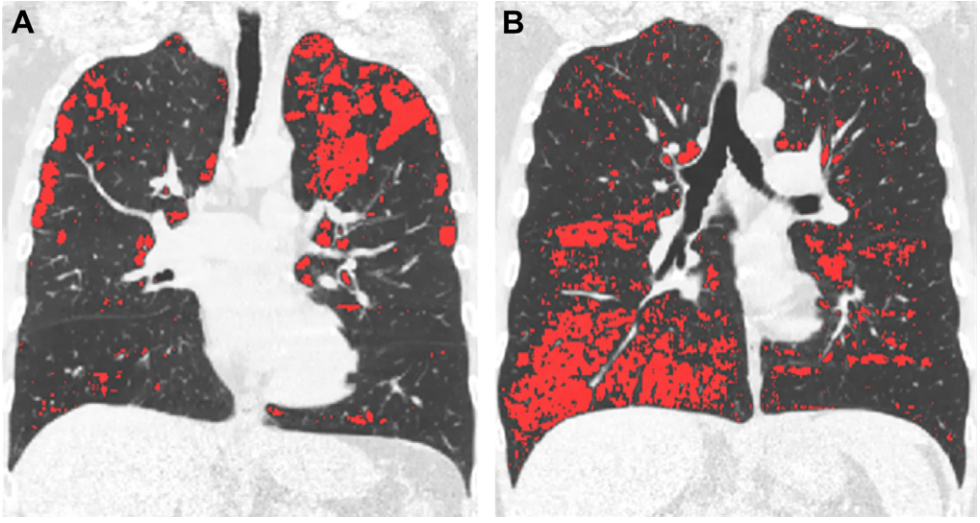

Figure 1 A) 62 Year old male subject, ES_{950} 9.0%, $FEV_1\% = 45\%$; Kco = 47%. B) 52 Year old male subject, ES_{950} 8.2%, $FEV_1\% = 112\%$; Kco = 83%.

The better perfusion and ventilation of the lower parts of the lungs compared to the perfusion and ventilation of the upper parts of the lungs can also result in a better compensation mechanism in the early stages of destruction, as in our study population. In cases of very severe emphysema, the healthy tissue cannot compensate for the destructed parts any more, resulting in severe pulmonary function impairment with a bad prognosis as reported in the NETT.[8]

For the spirometry, the role of small airway disease may be important. Kim et al. showed that that impact of upper zone emphysema on FEV_1/VC ratio is greater than the impact of lower zone emphysema, which may be caused by the difference in the degree of small airway disease (SAD).[16] While emphysema was not equally distribution throughout the lungs, a similar pattern can be expected for airway disease. Therefore, subjects with upper zone predominant emphysema may also have more severe small airway disease in their upper lobes, resulting in more airflow limitation.

Several other study groups have investigated the impact of emphysema distribution on severity of airflow limitation before, with conflicting results. Investigating 59 heavy smokers, Gurney et al. reported that the Tlco and TLC showed stronger correlations with basal emphysema than with apical emphysema, but the FEV_1 and FEF_{25-75} showed the highest correlations with apical emphysema. However, these differences were only significant for visually quantified emphysema, but not for extent of emphysema estimated by a computer. The authors hypothesized that a sampling bias may be a reason for the differences between both techniques. We used overlapping CT images, so sampling bias was not an issue in this study. The observation that we were able to demonstrate a small impact of distribution pattern of automated quantified CT emphysema on pulmonary function parameters in relatively healthy smokers may be due to the larger sample size. A study by Parr et al. in patients with α_1-antitrypsine deficiency showed that the $Tlco/V_A$ ratio was stronger influenced by upper zone emphysema and the FEV_1 by lower zone emphysema.[9] Interestingly, in a subsequent longitudinal study they reported that lower zone emphysema was associated with stronger progression in gas exchange impairment, while upper lobe predominant emphysema was associated with stronger decline in FEV_1.[3] These results indicate that progression over time is influenced by other factors than baseline results and may e.g. be stronger in areas that are less diseased at baseline due to spread of the disease throughout the lungs.

Saitoh et al. reported in a study in 62 subjects with a prior diagnosis of emphysema, that the FEV_1/VC showed the strongest correlations for with lower lung emphysema.[17] Haraguchi et al. included 25 subjects with known emphysema and reported that the Tlco correlated slightly better with middle and basal emphysema, while the FEV_1 showed the best correlation ($r = 0.64$) with basal emphysema only.[18] Nakano concluded in their study of 73 male patients with a prior diagnosis of COPD that the $Tlco/V_A$ was stronger influenced by upper-inner and middle-inner emphysema and the FEV_1/VC by lower-inner and lower-outer emphysema.[19] However Aziz et al. could not demonstrate any significant correlations in a retrospective study in 101 subjects with evidence of emphysema.[20]

These conflicting results show that the impact of emphysema distribution on lung function parameters is not clear yet and seem to be highly dependent on patient characteristics of the investigated study population (known emphysema or not, severity of airflow limitation, sample size and scanning technique). We included a large sample of study subjects and used volumetric data, excluding sample bias and power limitations.

Our study suffers from some limitations. The subjects included in the current analysis were relatively healthy. The subjects included in the NETT trial are severely diseased and in that cohort, distribution of emphysema has been shown to have an important impact on survival. Analyzing only more severe diseased subjects in our study sample did not show major changes in the reported results. The current analysis was a cross-sectional study, therefore we did not study the impact of distribution of emphysema on progression of disease and survival rate. Like in AATD patients, distribution of emphysema may have a different impact on progression of disease.

In conclusion, in contrast to the results reported for AATD patients, distribution pattern of emphysema in current and former heavy smokers has a small and likely not clinically relevant impact on lung function parameters, with slightly worse pulmonary function results for those with an apical predominance.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

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